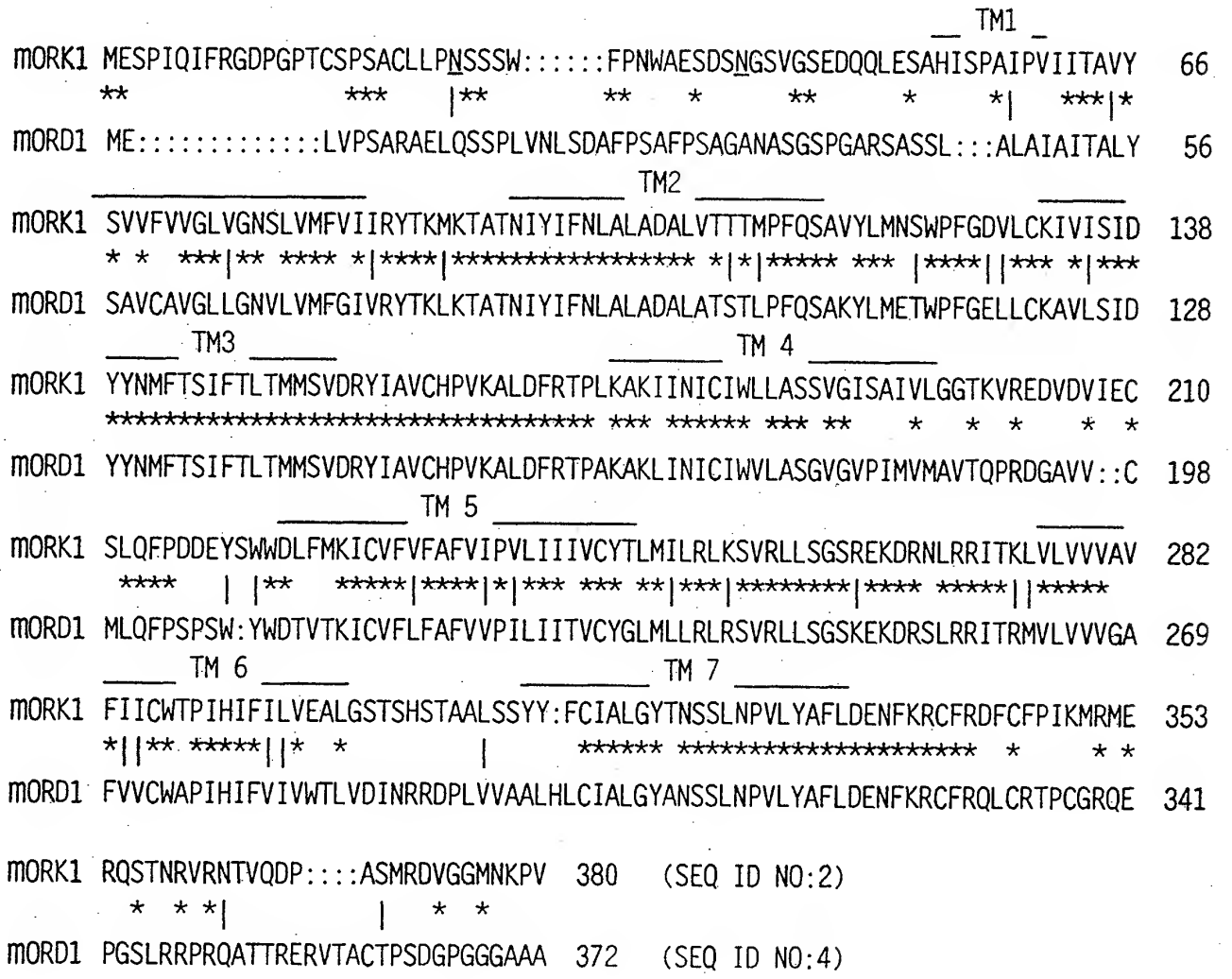


FIG. 1

REPLACEMENT SHEET

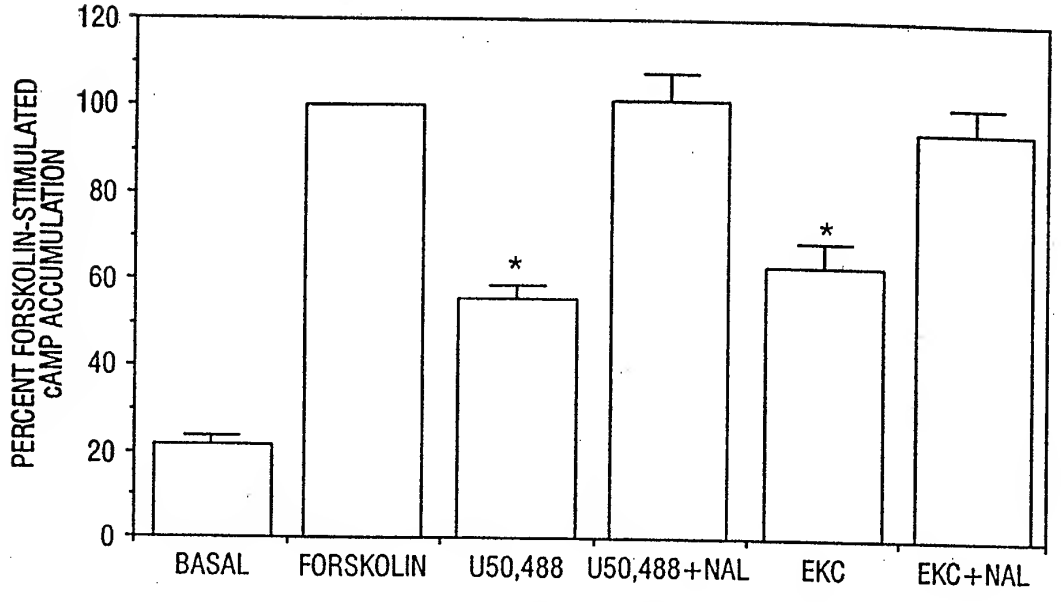

PERCENT FORSKOLIN-STIMULATED cAMP ACCUMULATION
120
100
80
60
40
20
0
*
*
BASAL
FORSKOLIN
U50,488
U50,488+NAL
EKC
EKC+NAL

FIG. 2A

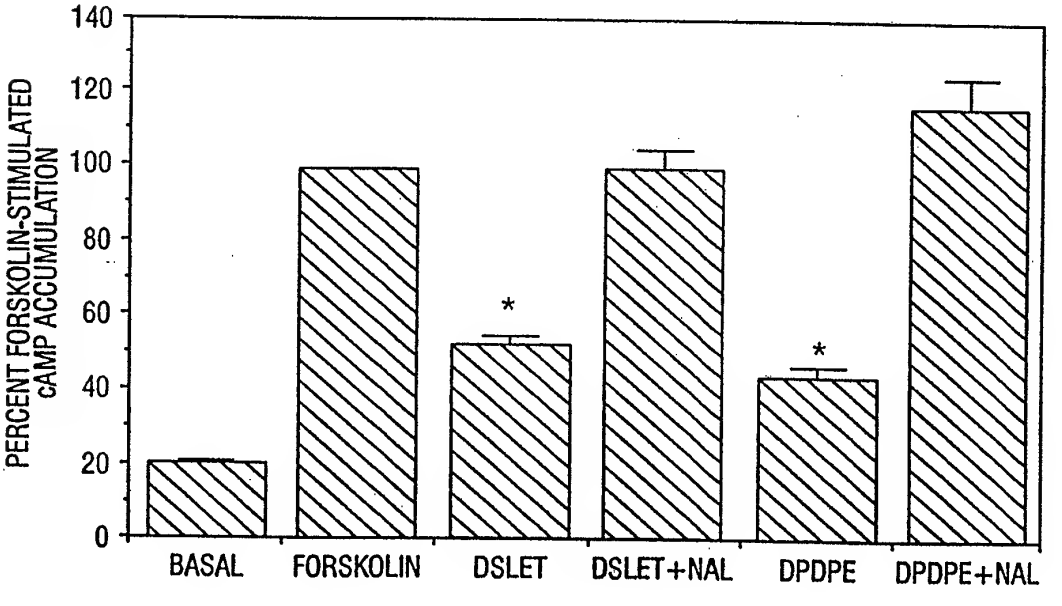

PERCENT FORSKOLIN-STIMULATED cAMP ACCUMULATION
140
120
100
80
60
40
20
0
*
*
BASAL
FORSKOLIN
DSLET
DSLET+NAL
DPDPE
DPDPE+NAL

FIG. 2B

```
1    AAGAAGCAAAATCAGTAATCCAAAGGCTATCACAAACACATTCACCTTATGGGGTTTGAC

                                                        TyrThrLysMetLysThrAla
61   TTGAAAATGGAGGGAAATGCTATTGTTTCTTTTCTTTTAGATACACAAAGATGAAGACAG

       ThrAsnIleTyrIlePheAsnLeuAlaLeuAlaAspAlaLeuValThrThrThrMetPro
121  CAACCAACATTTACATATTTAACCTGGCTTTGGCAGATGCTTTAGTTACTACAACCATGC

       PheGlnSerThrValTyrLeuMetAsnSerTrpProPheGlyAspValLeuCysLysIle
181  CCTTTCAGAGTACGGTCTACTTGATGAATTCCTGGCCTTTTGGGGATGTGCTGTGCAAGA

       ValIleSerIleAspTyrTyrAsnMetPheThrSerIlePheThrLeuThrMetMetSer
241  TAGTAATTTCCATTGATTACTACAACATGTTCACCAGCATCTTCACCTTGACCATGATGA

       ValAspArgTyrIleAlaValCysHisProValLysAlaLeuAspPheArgThrProLeu
301  GCGTGGACCGCTACATTGCCGTGTGCCACCCCGTGAAGGCTTTGGACTTCCGCACACCCT

       LysAlaLysIleIleAsnIleCysIleTrpLeuLeuSerSerSerValGlyIleSerAla
361  TGAAGGCAAAGATCATCAATATCTGCATCTGGCTGCTGTCGTCATCTGTTGGCATCTCTG
```

FIG. 3A

REPLACEMENT SHEET

```
      LysAlaLysIleIleAsnIleCysIleTrpLeuLeuSerSerSerValGlyIleSerAla
361   TGAAGGCAAAGATCATCAATATCTGCATCTGGCTGCTGTCGTCATCTGTTGGCATCTCTG

      IleValLeuGlyGlyThrLysValArgGluA
421   CAATAGTCCTTGGAGGCACCAAAGTCAGGGAAGGT:::::::::::::TTTCTGTGTTGT

                                    spValAspValIleGluCysCysLeuGlnPheProAsp
481   GGTTTTTATTGCCCTCCTCCAGACGTCGATGTCATTGAGTGCTGCTTGCAGTTCCCAGAT

      AspAspTyrSerTrpTrpAspLeuPheMetLysIleCysValPheIlePheAlaPheVal
541   GATGACTACTCCTGGTGGGACCTCTTCATGAAGATCTGCGTCTTCATCTTTGCCTTCGTG

      IleProValLeuIleIleIleValCysTyrThrLeuMetIleLeuArgLeuLysNNNVal
601   ATCCCTGTCCTCATCATCATCGTCTGCTACACCCTGATGATCCTGCGTCTCAAGANNGTC

      ArgLeuLeuSerGlySerArgGluLysAspNNNAsnLeuArgArgIleThrArgLeuVal
661   CGGCTCCTTTCTGGCTCCCGAGAGAAAGATNNCAACCTGCGTAGGATCACCAGACTGGTC
```

FIG. 3B

REPLACEMENT SHEET

```
      ArgLeuLeuSerGlySerArgGluLysAspNNNAsnLeuArgArgIleThrArgLeuVal
661   CGGCTCCTTTCTGGCTCCCGAGAGAAAGATNNCAACCTGCGTAGGATCACCAGACTGGTC

      LeuValValValAlaValPheValValCysTrpThrProIleHisIlePheIleLeuVal
721   CTGGTGGTGGTGGCAGTCTTCGTCGTCTGCTGGACTCCCATTCACATATTCATCCTGGTG

      GluAlaLeuGlySerThrSerHisSerThrAlaAlaLeuSerSerTyrTyrPheCysIle
781   GAGGCTCTGGGGAGCACCTCCCACAGCACAGCTGCTCTCTCCAGCTATTACTTCTGCATC

      AlaLeuGlyTyrThrAsnSerSerLeuAsnProIleLeuTyrAlaPheLeuAspGluAsn
841   GCCTTAGGCTATACCAACAGTAGCCTGAATCCCATTCTCTACGCCTTTCTTGATGAAAAC

      PheLysArgCysPheArgAspPheCysPheProLeuLysMetNNNMetGluArgNNNSer
901   TTCAAGCGGTGTTTCCGGGACTTCTGCTTTCCACTGAAGATGAGNATGGAGCGCNAGAGC


      ThrSerArgValArgAsnThrValGlnAspProAlaTyrLeuArgGluIleAspGlyMet
961   ACTAGCAGAGTCCGAAATACAGTTCAGGATCCTGCTTACCTGAGGGAGATCGATGGGATG

      MetAsnLysProValop                          (SEQ ID NO:12)
1021  ATGAATAAACCAGTATGACTAGTCGTGGA               (SEQ ID NO:11)
```

FIG. 3C

REPLACEMENT SHEET

	Met	Glu	Ser	Pro	Ile	Gln	Ile	Phe	Arg	Gly	Asp	Pro	Gly	Pro	Thr	Cys
	1				5				10						15	
	Ser	Pro	Ser	Ala	Cys	Leu	Leu	Pro	Asn	Ser	Ser	Ser	Trp	Phe	Pro	Asn
				20					25					30		
	Trp	Ala	Glu	Ser	Asp	Ser	Asn	Gly	Ser	Val	Gly	Ser	Glu	Asp	Gln	Gln
			35					40					45			
	Leu	Glu	Ser	Ala	His	Ile	Ser	Pro	Ala	Ile	Pro	Val	Ile	Ile	Thr	Ala
		50					55					60				
	Val	Tyr	Ser	Val	Val	Phe	Val	Val	Gly	Leu	Val	Gly	Asn	Ser	Leu	Val
	65					70					75					80
HUMAN							Tyr	Thr	Lys	Met	Lys	Thr	Ala	Thr	Asn	Ile
MOUSE	Met	Phe	Val	Ile	Ile	Arg	Tyr	Thr	Lys	Met	Lys	Thr	Ala	Thr	Asn	Ile
					85					90					95	

FIG. 4A-1

REPLACEMENT SHEET

```
HUMAN   Tyr Ile Phe Asn Leu Ala Leu Ala Asp Ala Leu Val Thr Thr Thr Met
MOUSE   Tyr Ile Phe Asn Leu Ala Leu Ala Asp Ala Leu Val Thr Thr Thr Met
                    100                 105                 110

HUMAN   Pro Phe Gln Ser Thr Val Tyr Leu Met Asn Ser Trp Pro Phe Gly Asp
MOUSE   Pro Phe Gln Ser Ala Val Tyr Leu Met Asn Ser Trp Pro Phe Gly Asp
            115                 120                 125

HUMAN   Val Leu Cys Lys Ile Val Ile Ser Ile Asp Tyr Tyr Asn Met Phe Thr
MOUSE   Val Leu Cys Lys Ile Val Ile Ser Ile Asp Tyr Tyr Asn Met Phe Thr
        130                 135                 140

HUMAN   Ser Ile Phe Thr Leu Thr Met Met Ser Val Asp Arg Tyr Ile Ala Val
MOUSE   Ser Ile Phe Thr Leu Thr Met Met Ser Val Asp Arg Tyr Ile Ala Val
145                 150                 155                 160

HUMAN   Cys His Pro Val Lys Ala Leu Asp Phe Arg Thr Pro Leu Lys Ala Lys
MOUSE   Cys His Pro Val Lys Ala Leu Asp Phe Arg Thr Pro Leu Lys Ala Lys
                    165                 170                 175
UMAN    Ile Ile Asn Ile Cys Ile Trp Leu Leu Ser Ser Ser Val Gly Ile Ser
MOUSE   Ile Ile Asn Ile Cys Ile Trp Leu Leu Ala Ser Ser Val Gly Ile Ser
                180                 185                 190
```

FIG. 4A-2

REPLACEMENT SHEET

HUMAN	Ala	Ile	Val	Leu	Gly	Gly	Thr	Lys	Val	Arg	Glu	Asp	Val	Asp	Val	Ile
MOUSE	Ala	Ile	Val	Leu	Gly	Gly	Thr	Lys	Val	Arg	Glu	Asp	Val	Asp	Val	Ile
			195					200					205			

HUMAN	Glu	Cys	Cys	Leu	Gln	Phe	Pro	Asp	Asp	Asp	Tyr	Ser	Trp	Trp	Asp	Leu
MOUSE	Glu	Cys	Ser	Leu	Gln	Phe	Pro	Asp	Asp	Glu	Tyr	Ser	Trp	Trp	Asp	Leu
		210					215					220				

HUMAN	Phe	Met	Lys	Ile	Cys	Val	Phe	Ile	Phe	Ala	Phe	Val	Ile	Pro	Val	Leu
MOUSE	Phe	Met	Lys	Ile	Cys	Val	Phe	Val	Phe	Ala	Phe	Val	Ile	Pro	Val	Leu
	225					230					235					240

HUMAN	Ile	Ile	Ile	Val	Cys	Tyr	Thr	Leu	Met	Ile	Leu	Arg	Leu	Lys	NNN	Val
MOUSE	Ile	Ile	Ile	Val	Cys	Tyr	Thr	Leu	Met	Ile	Leu	Arg	Leu	Lys	Ser	Val
					245					250					255	

HUMAN	Arg	Leu	Leu	Ser	Gly	Ser	Arg	Glu	Lys	Asp	NNN	Asn	Leu	Arg	Arg	Ile
MOUSE	Arg	Leu	Leu	Ser	Gly	Ser	Arg	Glu	Lys	Asp	Arg	Asn	Leu	Arg	Arg	Ile
				260					265					270		

FIG. 4A-3

REPLACEMENT SHEET

```
HUMAN   Thr Arg Leu Val Leu Val Val Val Ala Val Phe Val Val   Cys Trp Thr
MOUSE   Thr Lys Leu Val Leu Val Val Val Ala Val Phe Ile Ile Cys Trp Thr
                275                 280                 285

HUMAN   Pro Ile His Ile Phe Ile Leu Val Glu Ala Leu Gly Ser Thr Ser His
MOUSE   Pro Ile His Ile Phe Ile Leu Val Glu Ala Leu Gly Ser Thr Ser His
            290                 295                 300

HUMAN   Ser Thr Ala Ala Leu Ser Ser Tyr Tyr Phe Cys Ile Ala Leu Gly Tyr
MOUSE   Ser Thr Ala Ala Leu Ser Ser Tyr Tyr Phe Cys Ile Ala Leu Gly Tyr
305                 310                 315                 320

HUMAN   Thr Asn Ser Ser Leu Asn Pro Ile Leu Tyr Ala Phe Leu Asp Glu Asn
MOUSE   Thr Asn Ser Ser Leu Asn Pro Val Leu Tyr Ala Phe Leu Asp Glu Asn
                    325                 330                 335
```

FIG. 4B-1

REPLACEMENT SHEET

```
HUMAN   Phe Lys Arg Cys Phe Arg Asp Phe Cys Phe Pro Leu Lys Met NNN Met
MOUSE   Phe Lys Arg Cys Phe Arg Asp Phe Cys Phe Pro Ile Lys Met Arg Met
                    340                 345                 350

HUMAN   Glu Arg NNN Ser Thr Ser Arg Val Arg Asn Thr Val Gln Asp Pro Ala
MOUSE   Glu Arg Gln Ser Thr Asn Arg Val Arg Asn Thr Val Gln Asp Pro Ala
            355                 360                 365

HUMAN   Tyr Leu Arg Glu Ile Asp Gly Met Met Asn Lys Pro Val    (SEQ ID NO:12)
MOUSE     :  Ser Met Arg Asp Val Gly Gly Met Asn Lys Pro Val    (SEQ ID NO:2)
            370                 375                 380
```

FIG. 4B-2

REPLACEMENT SHEET

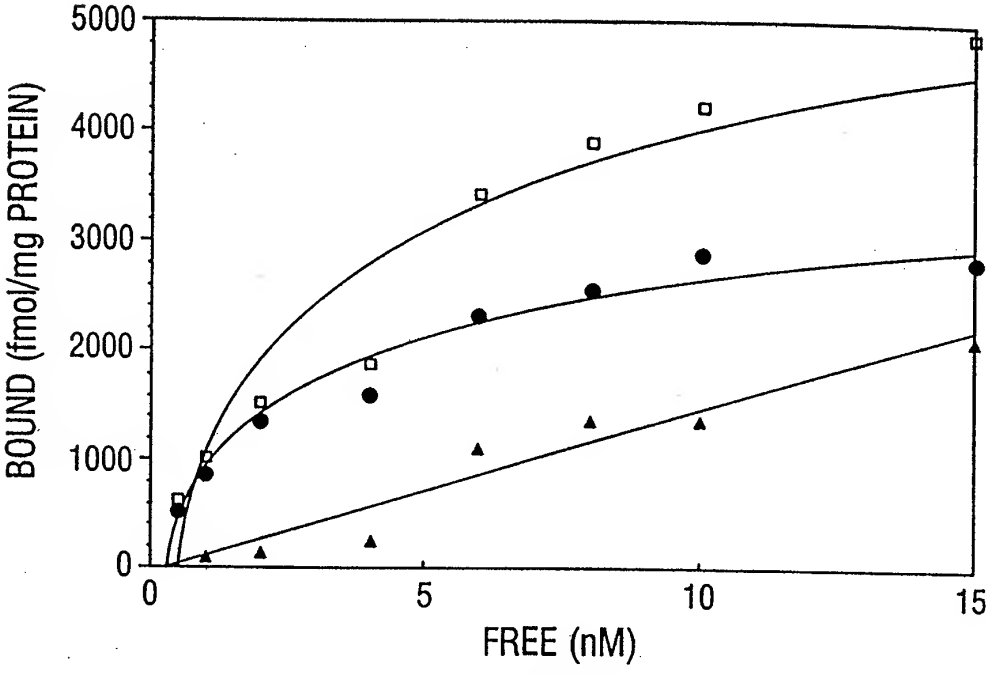

5000
4000
3000
2000
1000
0
BOUND (fmol/mg PROTEIN)
0
5
10
15
FREE (nM)

FIG. 5A

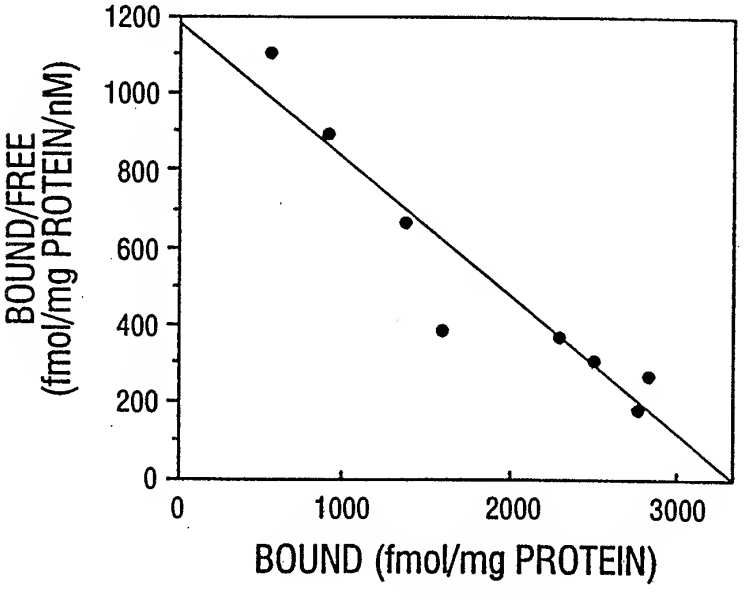

1200
1000
800
600
400
200
0
BOUND/FREE
(fmol/mg PROTEIN/nM)
0
1000
2000
3000
BOUND (fmol/mg PROTEIN)

FIG. 5B

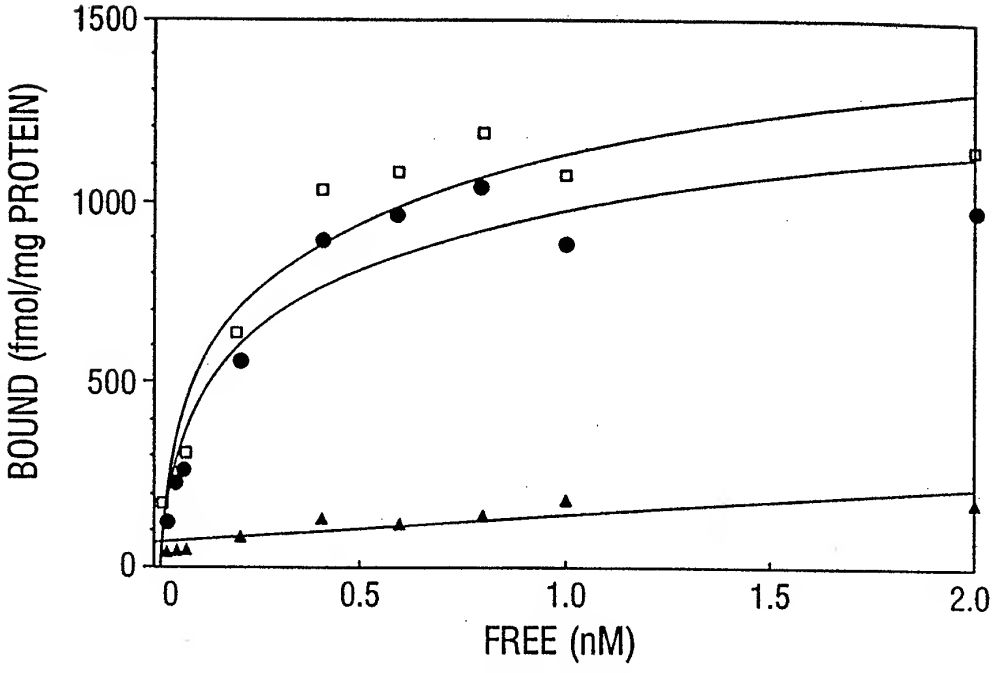

1500
1000
500
0
BOUND (fmol/mg PROTEIN)
0
0.5
1.0
1.5
2.0
FREE (nM)

FIG. 5C

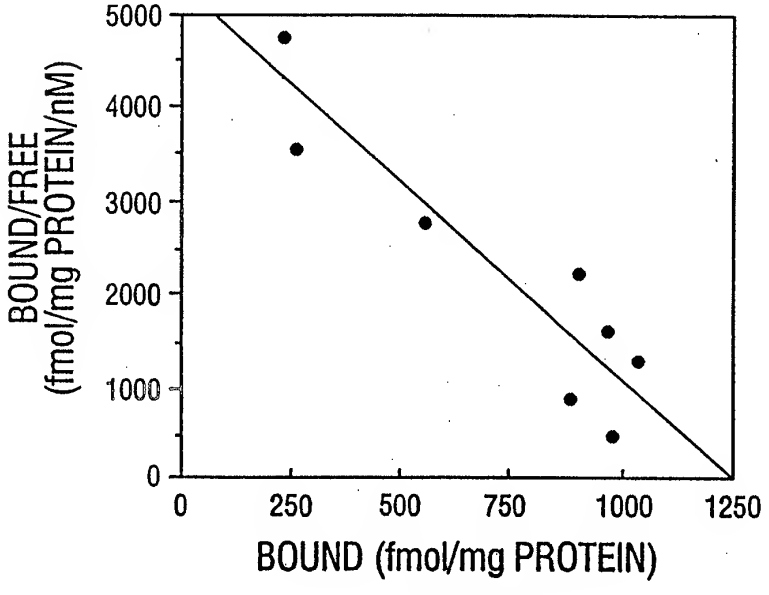

5000
4000
3000
2000
1000
0
BOUND/FREE
(fmol/mg PROTEIN/nM)
0
250
500
750
1000
1250
BOUND (fmol/mg PROTEIN)

FIG. 5D

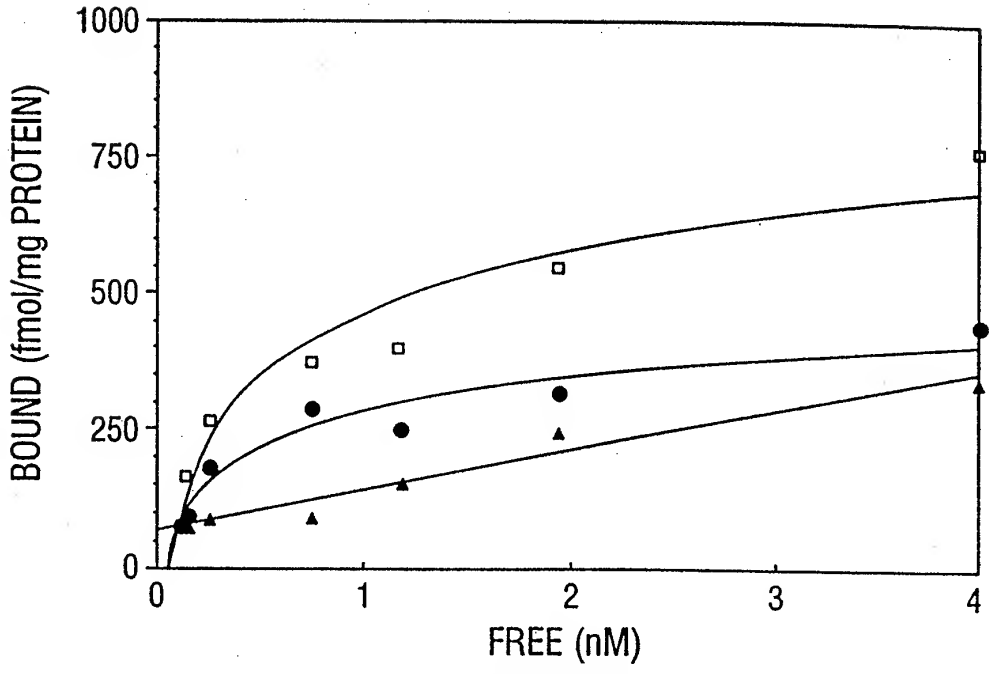

1000
750
500
250
0
BOUND (fmol/mg PROTEIN)
0
1
2
3
4
FREE (nM)

FIG. 5E

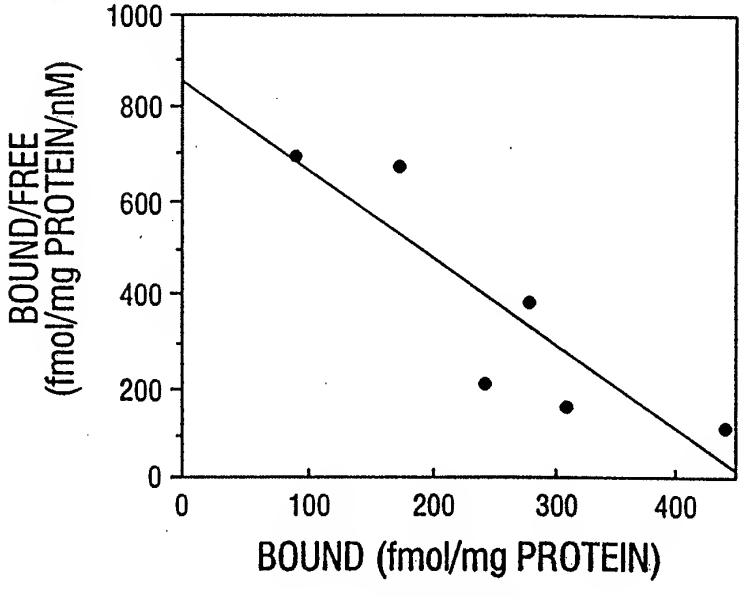

1000
800
600
400
200
0
BOUND/FREE
(fmol/mg PROTEIN/nM)
0
100
200
300
400
BOUND (fmol/mg PROTEIN)

FIG. 5F

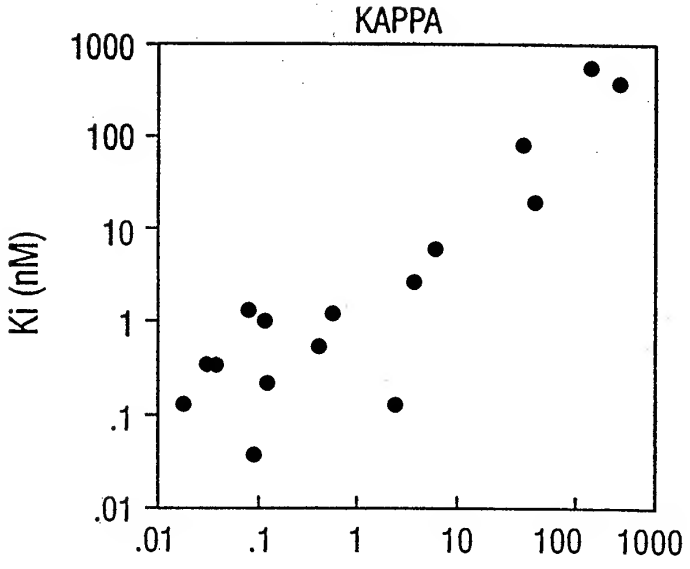

KAPPA
1000
100
10
1
.1
.01
Ki (nM)
.01
.1
1
10
100
1000

FIG. 6A

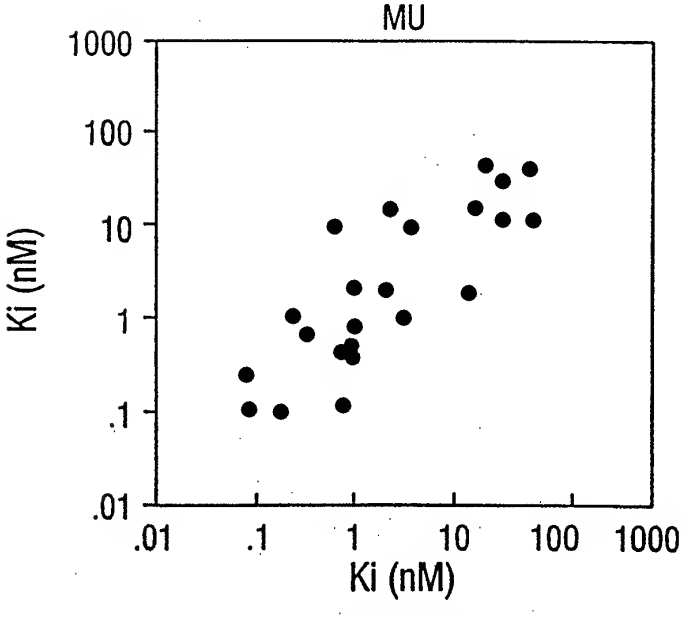

MU
1000
100
10
1
.1
.01
Ki (nM)
.01
.1
1
10
100
1000
Ki (nM)

FIG. 6B

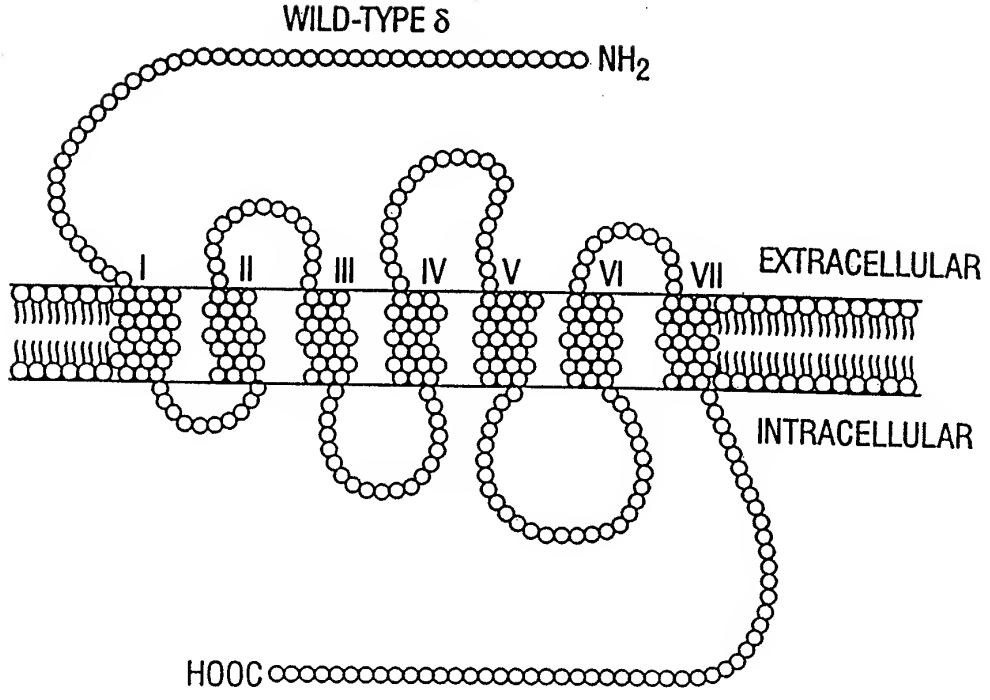

WILD-TYPE δ
NH2
I
II
III
IV
V
VI
VII
EXTRACELLULAR
INTRACELLULAR
HOOC

FIG. 7A

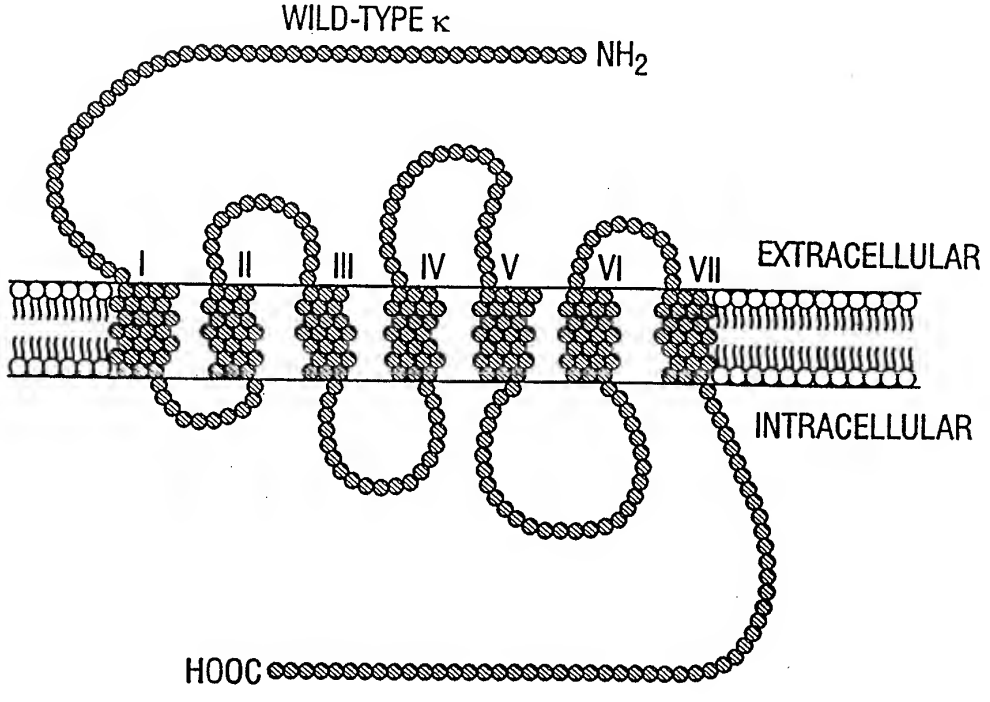

WILD-TYPE κ
NH2
I
II
III
IV
V
VI
VII
EXTRACELLULAR
INTRACELLULAR
HOOC

FIG. 7B

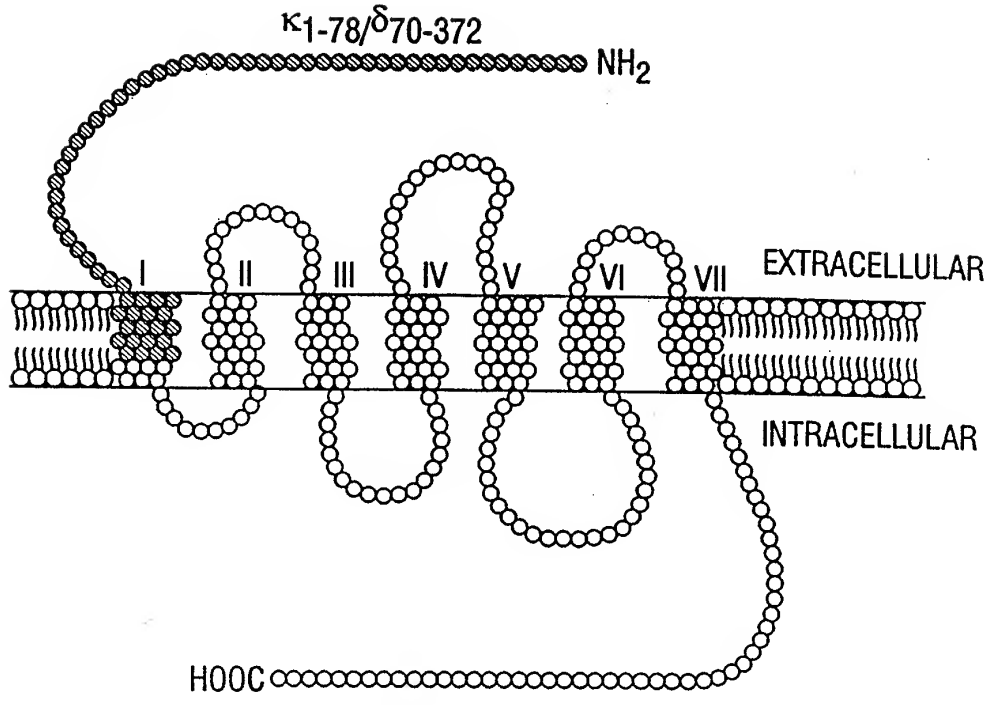

κ1-78/δ70-372
NH2
I
II
III
IV
V
VI
VII
EXTRACELLULAR
INTRACELLULAR
HOOC

FIG. 7C

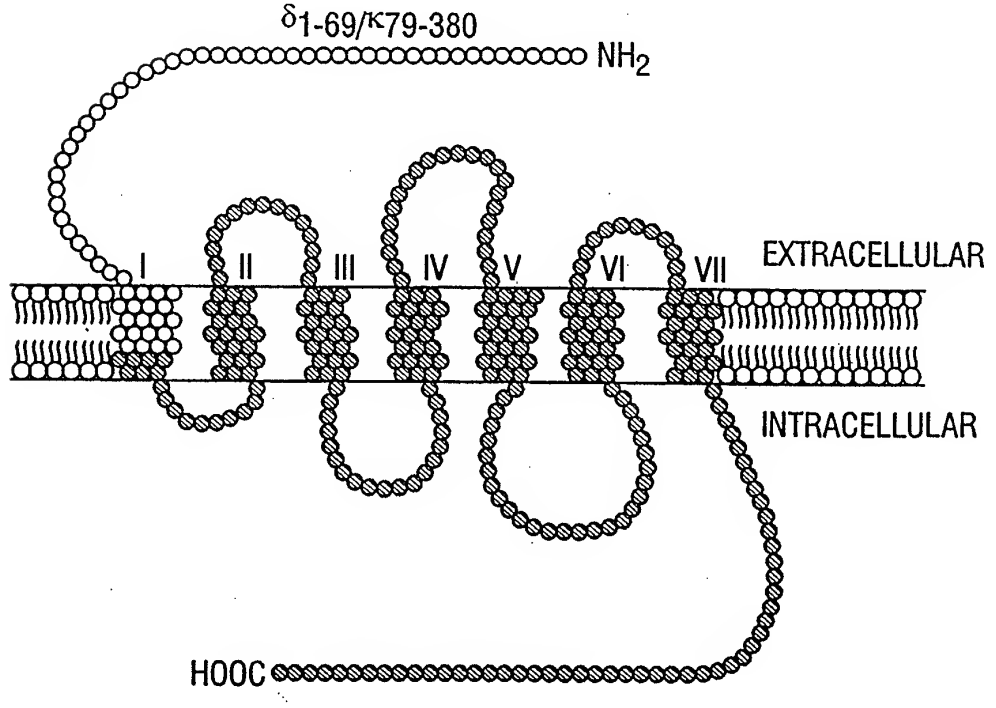

δ1-69/κ79-380
NH2
I
II
III
IV
V
VI
VII
EXTRACELLULAR
INTRACELLULAR
HOOC

FIG. 7D

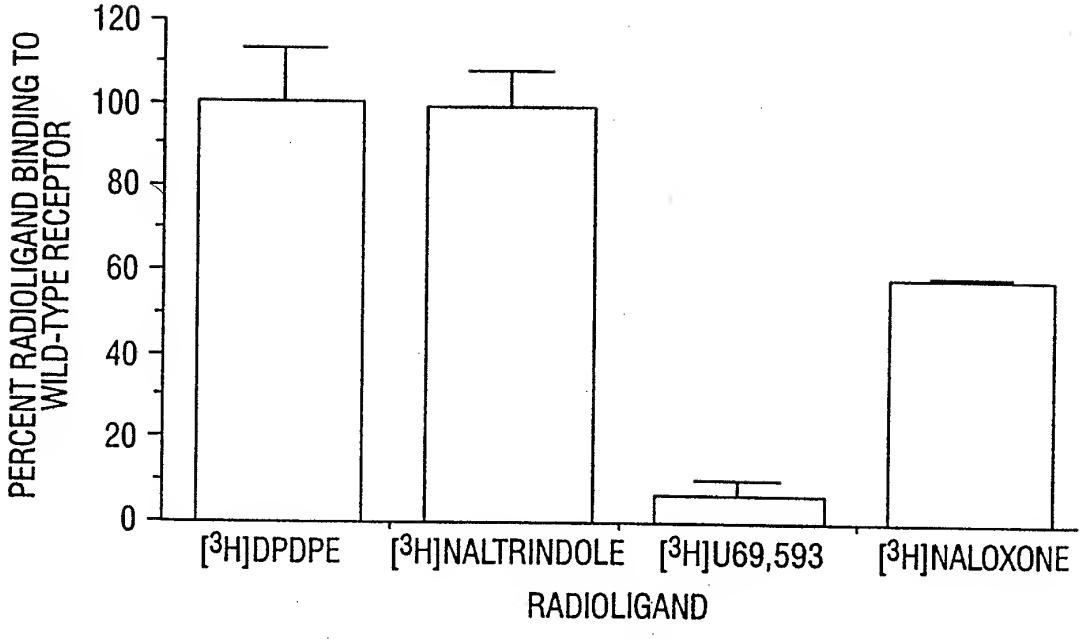

PERCENT RADIOLIGAND BINDING TO WILD-TYPE RECEPTOR
120
100
80
60
40
20
0
[3H]DPDPE
[3H]NALTRINDOLE
[3H]U69,593
[3H]NALOXONE
RADIOLIGAND

FIG. 8

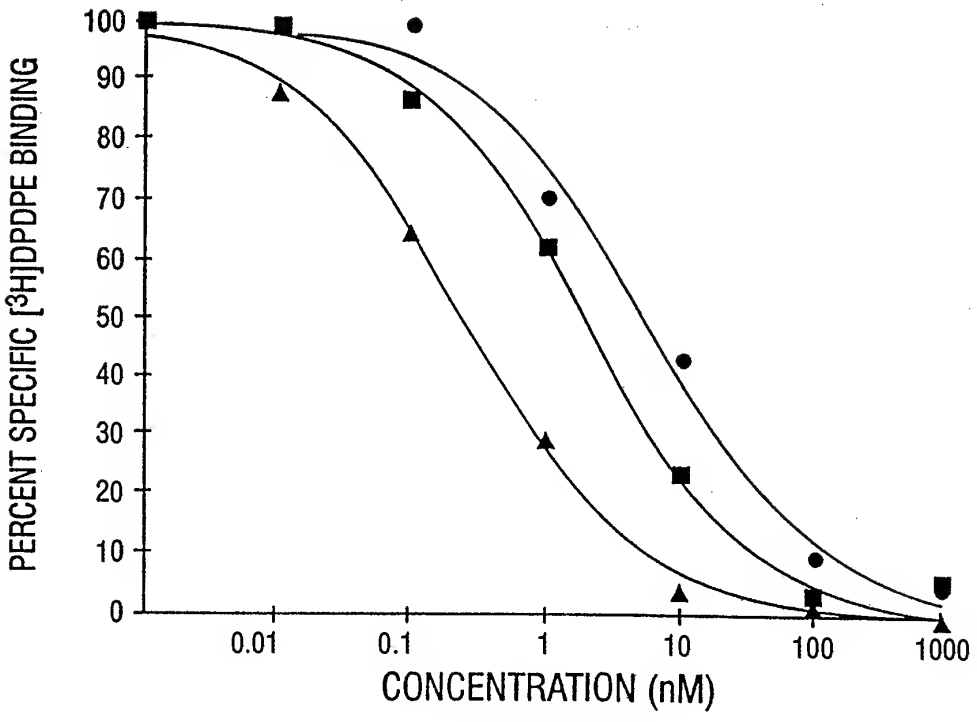

PERCENT SPECIFIC [3H]DPDPE BINDING
100
90
80
70
60
50
40
30
20
10
0
0.01
0.1
1
10
100
1000
CONCENTRATION (nM)

FIG. 9A

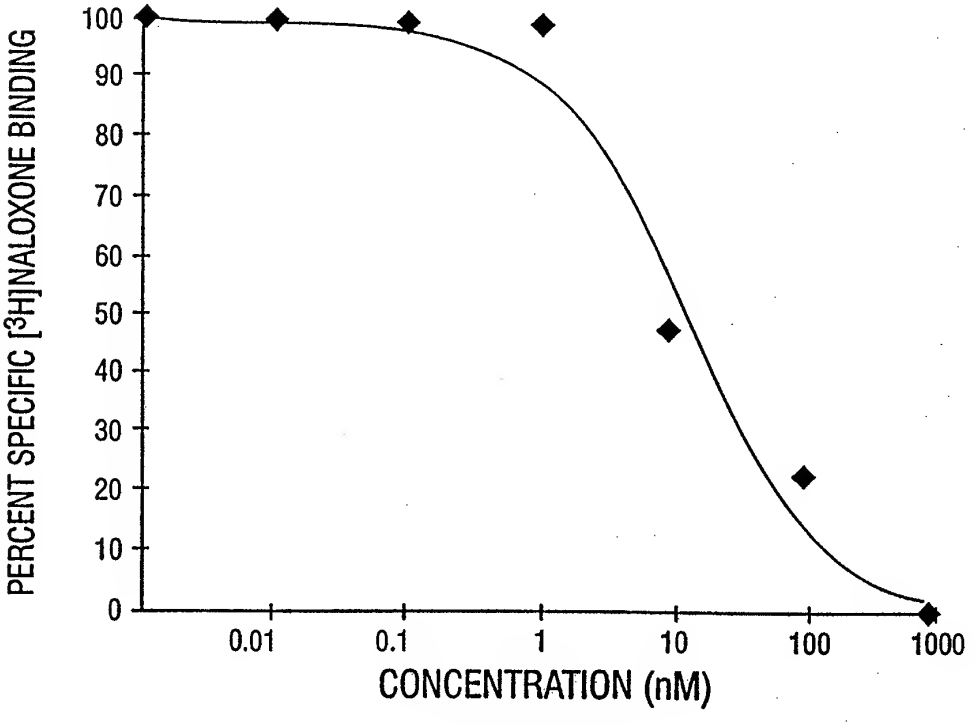

PERCENT SPECIFIC [3H]NALOXONE BINDING
100
90
80
70
60
50
40
30
20
10
0
0.01
0.1
1
10
100
1000
CONCENTRATION (nM)

FIG. 9B

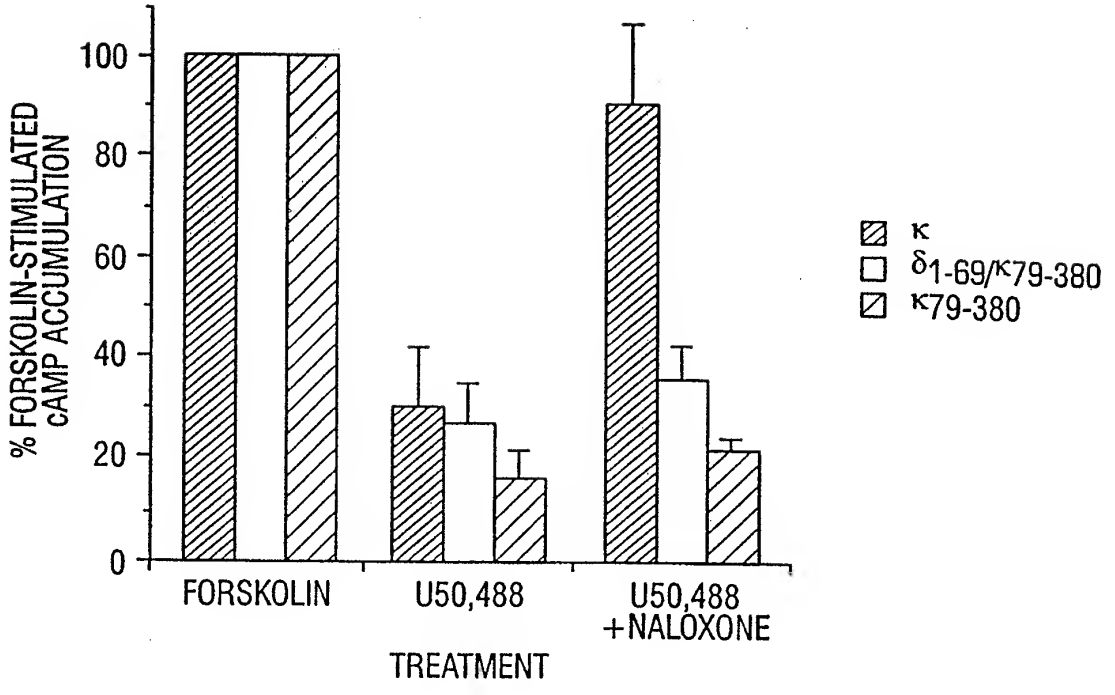


FIG. 10A

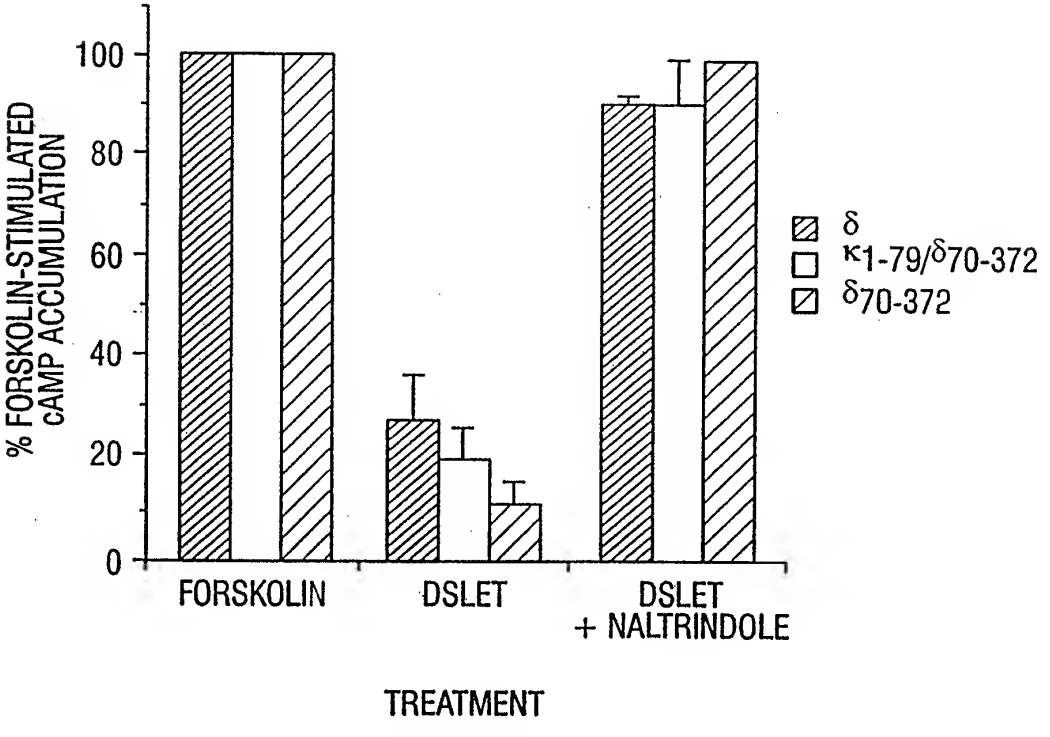


FIG. 10B

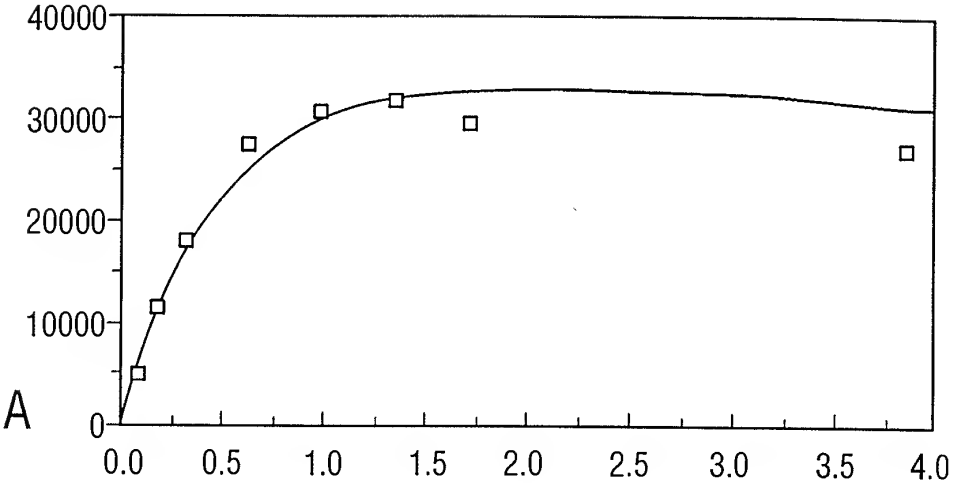


FIG. 11A

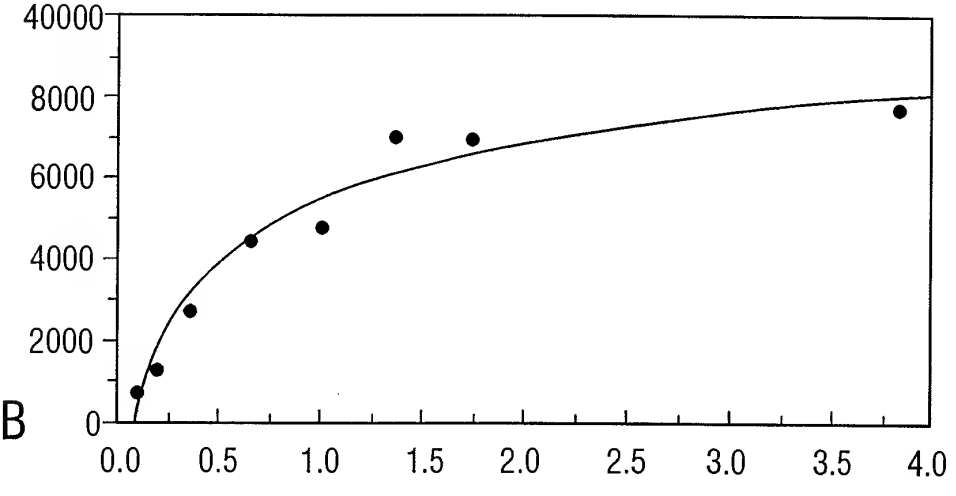


FIG. 11B

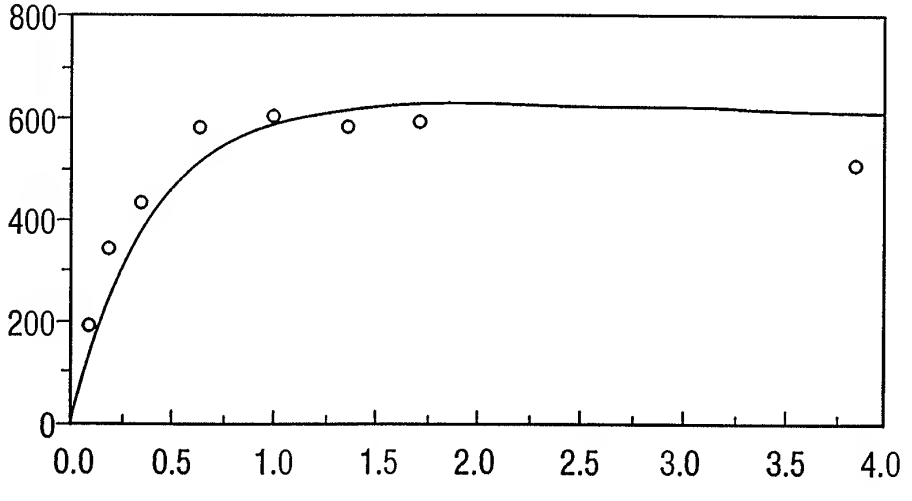


FIG. 11C

FIG. 12A

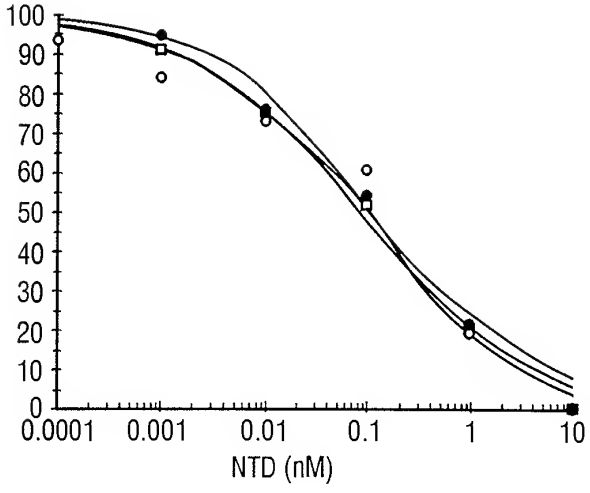


FIG. 12B

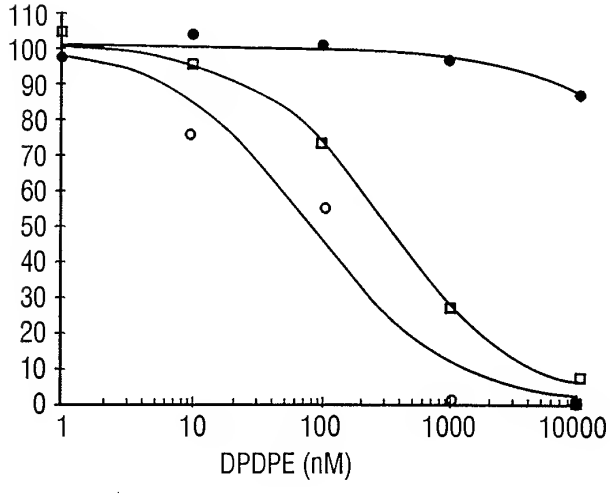
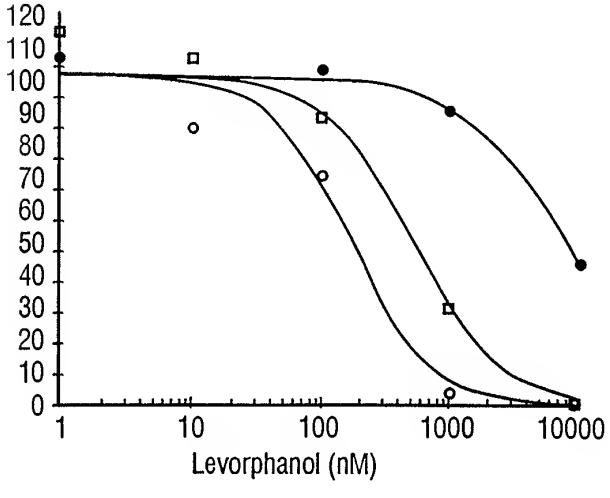


FIG. 12C



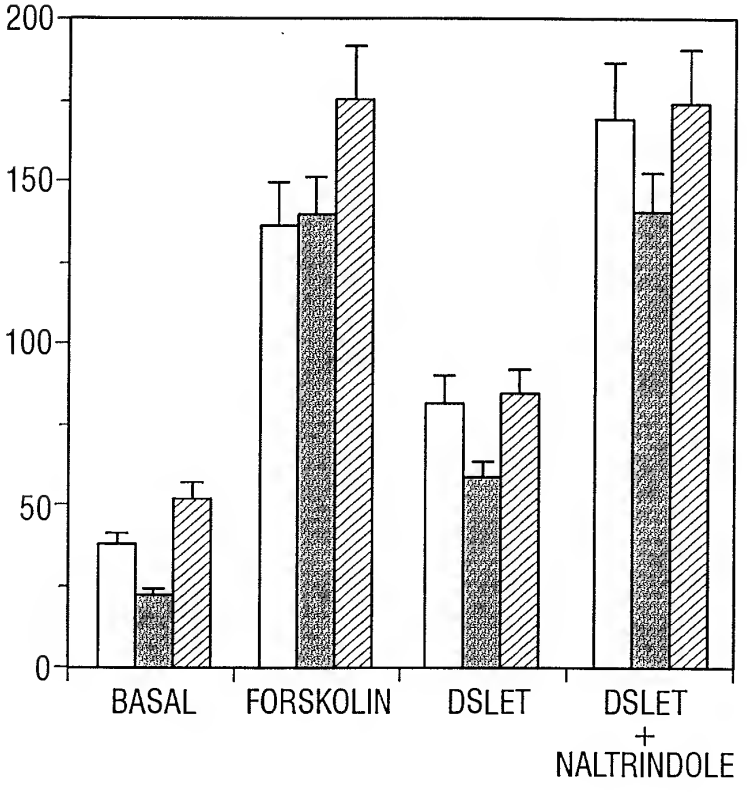


FIG. 13

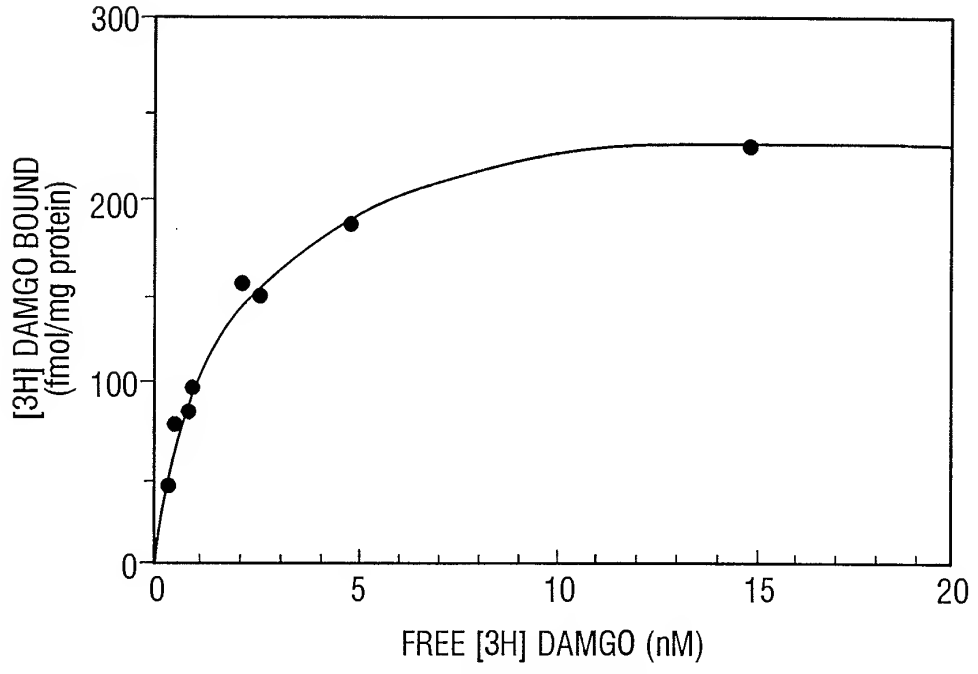


FIG. 14A

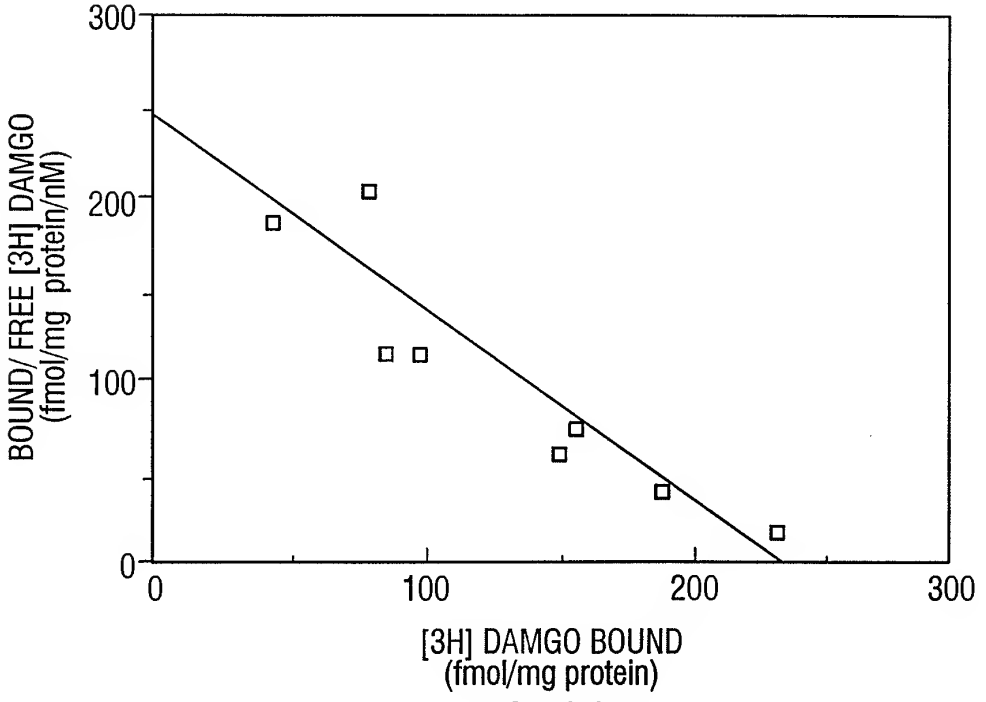


FIG. 14B

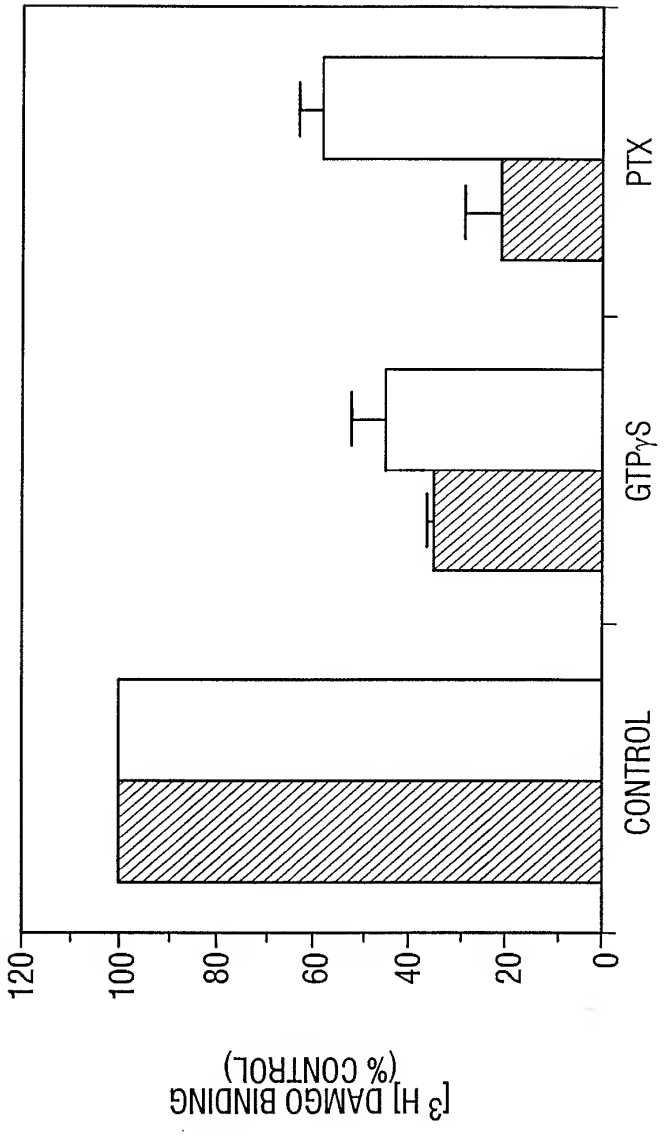

[3 H] DAMGO BINDING
(% CONTROL)
120
100
80
60
40
20
0
CONTROL
GTPγS
PTX

FIG. 15

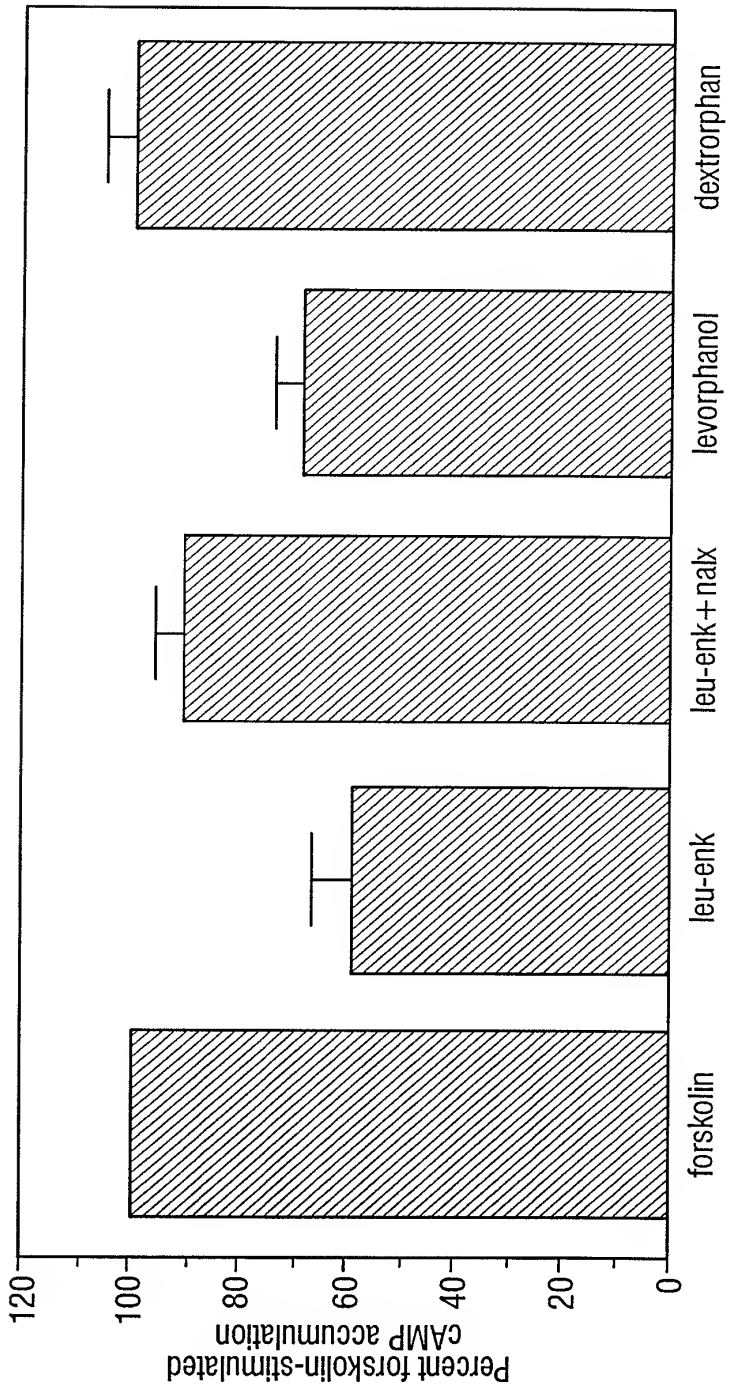

Percent forskolin-stimulated
cAMP accumulation
120
100
80
60
40
20
0
forskolin
leu-enk
leu-enk+nalx
levorphanol
dextrorphan

FIG. 16

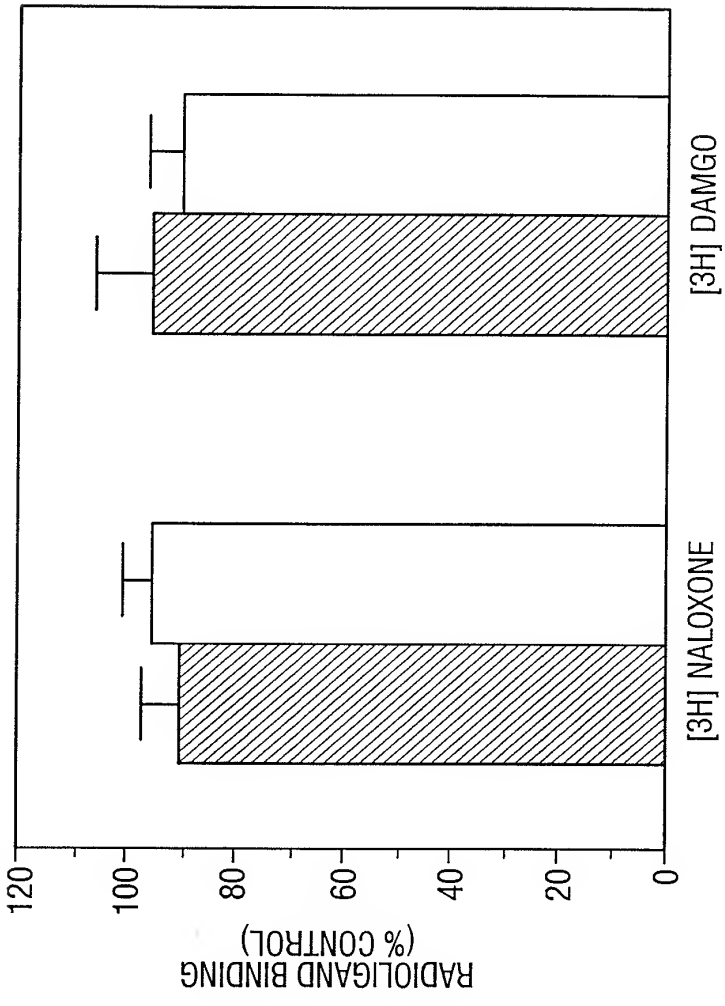

RADIOLIGAND BINDING
(% CONTROL)
120
100
80
60
40
20
0
[3H] NALOXONE
[3H] DAMGO

FIG. 17

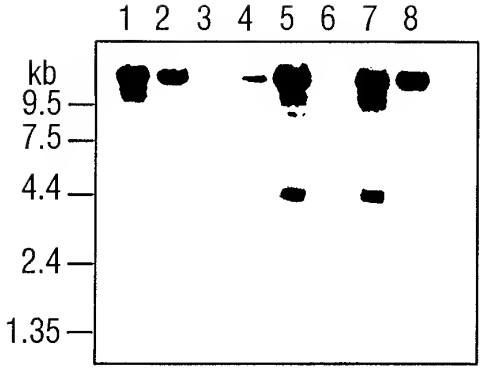


FIG. 18